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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,808	08/04/2003	Alexander V. Sokoloff	Mirus.014.04.1	8504

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EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,808	SOKOLOFF, A. ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-17,20-25 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-17,20-25 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to Amendment filed on May 3, 2005. Claims 2, 4, 18, 19, and 26 have been cancelled. Claims 1, 3, 5-17, 20-25, and 27-30 are currently pending and are under examination.

Withdrawal of Rejections

2. The rejection of claims 1, 20, 29, and 30 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn based on Applicants' amendment to the claims.

3. The rejection of claims 1, 12-15, and 22 under 35 U.S.C. 102(b) as being anticipated by Studier, F. (Virology 39: 562-574 (1969)) is withdrawn based on Applicants' amendment to the claims.

Maintenance of Rejections

Specification

4. The disclosure is objected to because of the following informalities: It appears as though the sentence, on page 43, beginning on line 14, should have the word, "to" prior to the word, "form". Appears to be intended to read, " These polymers may then be used to form ~~to~~ complexes with polynucleotides to facilitate delivery of the polynucleotide to hepatocytes."

Appropriate correction is required.

Claim Objections

5. Claims 1, 29, and 30 are objected to because of the following informalities:

6. The use of standard Markush language is suggested when describing members of a group. Suggest, for example in claim 1, "..said compound selected from the group ~~list~~ consisting of drug, complex, and polynucleotide."

7. In claim 1, suggest including implied use of targeting hepatocytes for the composition.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5-17, and 20-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In claims 1, 5-10, 29, and 30, when the compound is selected to be a complex, how is the compound covalently attached to the T7 ligand? On page 20, lines 19-22 of the specification, a "complex" is stated to form through non-covalent interactions, such as electrostatic, hydrogen bonding, and hydrophobic interactions.

11. Claims dependent on claim 1, do not cure the indefiniteness of the covalent attachment of a "complex", and are therefore rejected for depending on an indefinite claim 1.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 5-11, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The claims are drawn to a composition comprising a T7 ligand **covalently** attached to a compound, wherein the compound is selected from the group consisting of a drug, complex, and polynucleotide. The disclosure does not sufficiently describe compositions comprising a T7 ligand **covalently** attached to a compound, wherein the compound is selected from the group consisting of a drug, complex, and polynucleotide. Beginning on page 27, line 4, the disclosure describes a T7 p17 polypeptide ligand covalently attached to either an enhanced yellow fluorescent protein (EYFP) or interferon α2b. The fusion proteins are shown by confocal microscopy to be targeted to hepatocytes. Rather than describing covalently linked T7 ligands with liposomes, polyplex, lipopolyplex, and polynucleotides, which are targeted to hepatocytes, the specification describes association of T7 p17 ligands with liposomes, and polynucleotides through a non-covalent biotin-streptavidin interaction (see from page 30, line 24 through page 43, line 15). The disclosure does not sufficiently describe a composition comprising a T7 ligand **covalently** attached to a compound, wherein said compound is selected from the group consisting of a drug, complex, and a polynucleotide.

14. Claims 1, 5-11, 13, 16, 17, 20, 21, 22, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a composition comprising a T7 ligand covalently attached to a polypeptide, does not reasonably provide enablement for a composition comprising a T7 ligand covalently attached to any drug, complex, and polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to a composition comprising a T7 ligand covalently attached to a compound, wherein the compound is selected from the group consisting of a drug, complex, and polynucleotide. The disclosed compositions appear to have the conformational structures necessary to produce the inherent function/use of targeting hepatocytes.

2.) The breadth of the claims: the claims are extremely broad in that a very large number of constituents could be encompassed by both the T7 ligand, and the compound selected from the group consisting of a drug, complex, and polynucleotide.

3.) The predictability or unpredictability of the art: there is predictability in the art for conjugation of proteins with heterobifunctional groups, such as N-succinimidyl-3-[2-pyridyldithio]-propionamido (see Carlsson, J. et al. Biochem. J. 173: 723-737 (1978), entire document), but there is unpredictability in the art with regard to the ability to target hepatocytes based on the conjugation of any T7 ligand with any compound selected from the group consisting of drug, complex, and polynucleotide.

Sokoloff, A. et al. disclose the inactivation of T7 phage by natural IgM antibodies (see Sokoloff, A. et al. Molecular Therapy 2(2): 131-139 (2000), entire document, particularly page 135, section identified as Inactivation of Phage Requires Natural Antibodies). Thus, there is no way to predict whether the encompassed compositions comprising any T7 ligand covalently attached to any compound would be effective to use in targeting hepatocytes.

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the examples of T7 p17-EYFP and T7 p17-interferon fusion proteins do not in any way suggest that all of the encompassed compositions would have the conformations structures necessary to produce the inherent function of targeting hepatocytes. The specification provides guidance with respect to the covalent attachment of full-length proteins, EYFP, and interferon, discussed in the working examples, but provides no guidance whatsoever in selecting covalently attached liposomes, polyplex, lipopolyplex, and polynucleotides that could target hepatocytes.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which compounds, are capable of forming the requisite structure of a covalently attached T7 ligand with a compound selected from the group consisting of a drug, complex, and polynucleotide, because of the limited understanding between the correlation of the structure and the function/use of hepatocyte targeting.

7.) The state of the prior art: the prior art has shown "the use of natural ligand, i.e. asialofetuin, or synthetic ligands with galactosylated or lactosylated residues, such as galactosylated cholesterol, glycolipids, or galactosylated polymers has achieved significant targeting efficacy to the liver" (see Wu, J. et al., Frontiers in Bioscience 7, d717-725 (2002) Introduction). The asialoglycoprotein receptor on hepatocytes provides a target for cell specific drug and gene delivery. Rensen, P. et al. disclose the upper size limit for uptake and processing of ligands by the Asialoglycoprotein receptor on hepatocytes *in vitro* and *in vivo*. Rensen, P. et al. disclose the asialoglycoprotein receptor (ASGPr) can bind and uptake liposomes with a diameter of 70 nm, whereas larger particles do not bind to the ASGPr (Rensen, P. et al. Journal

of Biological Chemistry 276(40): 37577-37584 (2001), see page 37578, last paragraph of Introduction).

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Studier et al. (Methods in Enzymology 185: 60-89 (1990)). Studier et al. disclose a fusion protein comprising a T7 ligand covalently attached to a drug. A polypeptide sequence is reasonably interpreted to be a drug, based on the disclosure of the application (see page 13, lines 1-3, and page 18, lines 2+). Furthermore, interferon is a polypeptide sequence that is disclosed as a drug. Therefore, Studier et al. disclose a fusion protein comprising the first 11 amino acids of the gene 10 protein of T7 (see page 75, 1st paragraph, current application, claim 1).

Claim Rejections - 35 USC § 102/Claim Rejections - 35 USC § 103

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1, and 3 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sim, G-K. et al. (U.S. Patent 6,471,957 B1) in view of Lutz-Freyermuth, C. et al. (PNAS 87:6393-6397 (1990)).

20. Sim, G-K. et al. disclose a fusion protein that comprises a T7 ligand with interferon. Sim, G-K. et al. disclose in one embodiment of the invention a fusion protein that includes feline interferon alpha attached to one or more fusion segments. A preferred fusion segment includes a T7 tag peptide (see col. 22, lines 29-col. 23, line 11). Sim, G-K. et al. do not explicitly disclose a particular T7 tag peptide sequence.

Lutz-Freyermuth, C. et al. disclose an epitope tag representing 12 amino acids of phage T7 gene 10 protein (see Results, page 6395, 1st sentence in section identified as Reconstitution and Immunoprecipitation of RNA-Protein Complexes). A person of ordinary skill in the art

would have been motivated to use the epitope tag disclosed by Lutz-Freyermuth, C. et al. to improve recombinant protein purification. Therefore, it would have been obvious to the person having ordinary skill in the art to use the epitope tag disclosed by Lutz-Freyermuth, C. et al. in the interferon fusion protein disclosed by Sim, G-K. et al., because Sim, G-K. et al. disclose the use of a T7 tag peptide sequence.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 4, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER